Increased arterial stiffness is closely associated with hyperglycemia and improved by glycemic control in diabetic patients

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ABSTRACT

Aims/Introduction: Although arteriosclerotic diseases have been reported to be frequently complicated by diabetes mellitus (DM), a detailed relationship between hyperglycemia and arterial stiffness has not been fully clarified. We investigated the influence of hyperglycemia on arterial stiffness using the cardio-ankle vascular index (CAVI), which is a new method for estimating arterial stiffness.

Materials and Methods: CAVI values of 52 early-staged DM patients (duration <5 years, no microangiopathies) were compared with those of 43 age-matched non-diabetic (NDM) subjects. The association between CAVI and clinical background factors was evaluated. The effect of glycemic improvement on CAVI was examined in 36 DM patients who were hospitalized for 2 weeks to treat hyperglycemia. CAVI and clinical parameters were measured twice during hospitalization and again after 8 weeks. Additionally, we measured CAVI before and 2 h after breakfast in five DM and five NDM subjects.

Results: The CAVI of DM patients was significantly higher than that of NDM subjects. Multiple regression analysis showed that neither hypertension, obesity nor dyslipidemia, but aging and hemoglobin A1c (HbA_{1c}) were significantly related to CAVI elevation. The CAVI, HbA_{1c} and total cholesterol (TC) had significantly improved. Improvement of CAVI was significantly associated with HbA_{1c} improvement. In contrast, no significant association was observed between the improvements of TC and CAVI. CAVI values before and after breakfast did not change significantly.

Conclusions: CAVI elevation seems to be a sensitive arteriosclerotic marker, which is closely associated with hyperglycemia and improved by glycemic control. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2012.00229.x, 2013)

INTRODUCTION

The age of death in Japanese patients with diabetes mellitus (DM) is 10 years younger than the general population, and the second most common cause of death is vascular disease[1]. To improve the prognosis of DM patients, early diagnosis of arteriosclerosis is important. Arterial stiffness is recognized as an early arteriosclerotic index in DM patients[2]. The cardio-ankle vascular stiffness index (CAVI) has recently been used as an index that reflects arterial stiffness[3–5]. We have previously reported that the CAVI measures arterial stiffness independent of blood pressure[6]. Increased arterial stiffness has been reported to be complicated by metabolic syndrome[7], sleep apnea syndrome[8] and smoking[9]. However, a detailed relationship between hyperglycemia and arterial stiffness has not been fully clarified.

In the present study, we investigated the clinical factors that were related to CAVI in patients with DM of short duration and no microangiopathies. Furthermore, the effect of glycemic control on CAVI was also examined.

MATERIALS AND METHODS

Arterial Stiffness in the Early Stage of Diabetes

We measured CAVI in 52 DM patients (five type 1 and 47 type 2 diabetic) with DN of short duration (<5 years) without microangiopathies and 43 age-matched non-diabetic (NDM) subjects. In DM patients, 15 were outpatients and 37 were inpatients of the Wakayama Medical University Hospital. As many patients had been hospitalized for glycemic control, two-thirds of the patients were under insulin treatment. Then we compared clinical factors, such as sex, age, body mass index (BMI), blood pressure (BP), hemoglobin A1c (HbA_{1c}), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL), smoking habit, ankle brachial pressure index (ABI) and CAVI between the two groups (Table 1). Participants with a low ABI <0.9 were excluded. HbA_{1c} (%) was

Table 1 | Comparison of clinical characteristics and arteriosclerotic indices between non-diabetic and diabetic participants

Clinical background	NDM	DM	P-value
n	43	52	
Sex (male/female)	35/8	26/26	0.002
Age (years)	43.0 ± 6.4	44.5 ± 10.0	0.403
Duration of diabetes mellitus (years)		2.4 ± 1.7	
Therapy (diet and exercise/OHA/insulin)		5/12/35	
Body mass index (kg/m^2)	24.2 ± 3.6	24.4 ± 4.0	0.784
Systolic BP (mmHg)	124 ± 15	121 ± 14	0.283
Diastolic BP (mmHg)	79 ± 9	78 ± 9	0.494
Hypertension (%)	37.2	28.8	0.387
HbA$_{1c}$ (%)	5.3 ± 0.3	9.6 ± 2.3	<0.001
Total cholesterol (mg/dL)	200 ± 30	193 ± 74	0.572
Triglyceride (TG: mg/dL)	138 ± 101	195 ± 156	0.049
HDL-C (mg/dL)	61 ± 15	48 ± 11	<0.001
Dyslipidemia (%)	53.5	61.5	0.429
Smoking, % (n/total number)	35.5 (11/31)	36.0 (18/50)	0.962
Arteriosclerotic indices			
Right ABI	1.12 ± 0.10	1.13 ± 0.11	0.497
Left ABI	1.11 ± 0.10	1.12 ± 0.09	0.445
Mean ABI	1.11 ± 0.09	1.13 ± 0.09	0.435
Right CAVI	6.59 ± 0.64	7.00 ± 1.12	0.035
Left CAVI	6.62 ± 0.65	7.03 ± 1.06	0.029
Mean CAVI	6.61 ± 0.63	7.02 ± 1.08	0.031
Ultrasonography of the carotid artery			
n	20	33	
Right IMT (mm)	0.67 ± 0.19	0.71 ± 0.13	0.377
Left IMT (mm)	0.75 ± 0.17	0.74 ± 0.17	0.748
Mean IMT (mm)	0.73 ± 0.16	0.72 ± 0.13	0.948
Prevalence of atherosclerotic plaque (%)	60.0	60.6	0.965

Values are presented as mean ± SD. Mean indicates the average of left and right. Hemoglobin A1c (HbA$_{1c}$; %) was estimated as a National Glycohemoglobin Standardization Program equivalent value. ABI, ankle brachial pressure index; BP, blood pressure; CAVI, cardio-ankle vascular index; DM, diabetes mellitus group; HDL-C, high-density lipoprotein cholesterol; IMT, intima-media complex thickness; NDM, non-diabetes mellitus group; OHA, oral hypoglycemic agents.

estimated as a National Glycohemoglobin Standardization Program equivalent value (%) calculated by the formula HbA$_{1c}$ (%) = HbA$_{1c}$ (JDS) (%) + 0.4%[10]. Hypertension was defined by a blood pressure >140/85 mmHg or antihypertensive treatment. Participants with TC >220 mg/dL and/or TG >150 mg/dL and/or HDL <40 mg/dL or those on antihyperlipidemic medication were defined as dyslipidemic.

Ultrasonography of the carotid artery was carried out in 33 DM and 20 NDM participants. Intima-media complex thickness of artery (IMT) and atherosclerotic plaque was compared between the two groups. The association between the CAVI and clinical background factors including age, sex, BMI, hypertension and dyslipidemia were evaluated by multiple regression analysis (model 1). Additional analyses that added smoking as an independent variable were also carried out (model 2).

Effect of Glycemic Control on Arterial Stiffness

We measured CAVI in 36 DM patients (five type 1 and 31 type 2 diabetic) who were hospitalized for 2 weeks for glycemic control and diabetes education. As many patients had been hospitalized for the improvement of hyperglycemia, 86% (31/36) of the patients had been treated with insulin. After 8 weeks, the CAVI was re-examined to evaluate the influence of glycemic control on CAVI. The association between the change of clinical characteristics and arteriosclerotic indices was also evaluated. Furthermore, we measured the CAVI before and 2 h after breakfast in five DM and five NDM participants to examine the influence of very short-term blood glucose change on CAVI.

Methods of Measuring Arteriosclerotic Indices

CAVI and ABI were measured using a pulse wave analyzer, VaSera VS-1000 (Fukuda Denshi, Tokyo, Japan). ABI and CAVI represent the degree of vascular stenosis and the stiffness of the arterial wall in one examination, respectively. The arteries measured for arterial stiffness included both elastic and muscular arteries. Details were described previously[3,6]. Left, right and mean (the average of left and right) values were evaluated.

To evaluate IMT and plaque, ultrasonography was carried out with a Power Vision 7000 TM (Toshiba, Tokyo, Japan). IMT of the carotid artery was measured at three sites, and an average was used for analysis. Plaque was defined as a circumscribed elevated lesion ≥ 1.1 mm in thickness[11,12].

Statistical Analyses

Data are shown as mean ± standard deviation (SD). Differences in the average data and the prevalence of clinical background factors between non-diabetic and diabetic participants were statistically analyzed by an unpaired t-test and a chi-square test, respectively. Serial changes of the data were statistically analyzed by a paired t-test. The associations between the CAVI and clinical background factors were evaluated by multiple regression analyses. Statistical analyses were carried out using statistical software (Statview-J5.0TM; Hulinks, Tokyo, Japan). $P < 0.05$ was accepted as statistically significant.

RESULTS

Arterial Stiffness in the Early Stage of Diabetes

In the DM group, HbA$_{1c}$ and TG were significantly higher, and HDL was lower compared with the NDM group. Although ABI, IMT and prevalence of plaque did not show a significant difference between the DM and NDM groups, right, left and mean CAVI of the DM group were significantly higher than

Table 2 | Relationships between cardio-ankle vascular index and clinical characteristics in 95 diabetic and non-diabetic participants evaluated by multiple regression analysis

	Model 1		Model 2	
	Dependent variables		Dependent variables	
	Mean CAVI	Higher CAVI	Mean CAVI	Higher CAVI
Case number	95	95	81	81
Decision coefficient (R^2)	0.337	0.338	0.377	0.376
P-value	<0.0001	<0.0001	<0.0001	<0.0001
Independent variables	β (*P*-value)	β (*P*-value)	β (*P*-value)	β (*P*-value)
Age (years)	0.544 (<0.001)	0.536 (<0.001)	0.578 (<0.001)	0.568 (<0.001)
Sex (female: 0, male: 1)	0.173 (0.067)	0.177 (0.060)	0.275 (0.012)	0.281 (0.010)
Body mass index (kg/m^2)	−0.123 (0.212)	−0.123 (0.213)	−0.110 (0.298)	−0.112 (0.291)
HbA$_{1c}$ (%)	0.180 (0.049)	0.192 (0.036)	0.198 (0.046)	0.206 (0.039)
Hypertension (no: 0, yes: 1)	−0.049 (0.619)	−0.024 (0.809)	−0.101 (0.319)	−0.075 (0.462)
Dyslipidemia (no: 0, yes: 1)	0.013 (0.888)	0.020 (0.833)	0.045 (0.665)	0.052 (0.621)
Smoking (no: 0, yes: 1)			−0.103 (0.320)	−0.099 (0.340)

Mean cardio-ankle vascular index (CAVI) indicates the average of left and right CAVI. Higher CAVI means the higher one in the right and left CAVI. β, standard regression coefficient.

those of the NDM group (Table 1). The male ratio of the DM group was significantly higher than that of the NDM group. When mean CAVI values were separately compared between males and females, CAVI in male DM patients were significantly higher than that in male NDM participants (7.3 ± 1.1 vs 6.6 ± 0.7, $P = 0.003$), but CAVI in female diabetic patients was not different from that in female NDM participants (6.7 ± 1.0 → 6.8 ± 0.4, $P = 0.646$).

Right, left and mean CAVI of 33 DM patients who underwent carotid ultrasonography were also significantly higher than those of 20 NDM participants who received carotid ultrasonography (6.77 ± 0.85 vs 6.31 ± 0.70, $P = 0.048$; 6.85 ± 0.84 vs 6.34 ± 0.73, $P = 0.028$; 6.81 ± 0.84 vs 6.32 ± 0.70, $P = 0.034$, respectively). Multiple regression analysis showed a significant relationship between mean and higher CAVI and age and HbA$_{1c}$ (Table 2, model 1). Virtually the same result was obtained from the reanalysis to which smoking was added as an independent variable (Table 2, model 2).

Effect of Glycemic Control on Arterial Stiffness

After hospitalization, HbA$_{1c}$, TC, right, left and mean CAVI were significantly improved (Table 3). To know which of these factors, HbA$_{1c}$ or TC, is more closely associated with CAVI improvement, we divided participants into two groups according to the change of HbA$_{1c}$ (HbA$_{1c}$) and TC, and then CAVI changes were compared between each groups (Figure 1). Although CAVI of the well-improved HbA$_{1c}$ group (HbA$_{1c}$ 1%) had significantly decreased (8.1 ± 1.3 → 7.4 ± 1.4, $P < 0.001$), CAVI of the poorly improved group (HbA$_{1c}$ < 1%) had not significantly decreased (8.7 ± 1.1 → 8.5 ± 1.2, $P = 0.416$). In contrast, CAVI of both groups whose TC had

decreased and those with no change/increase was significantly reduced by hospitalization (8.0 ± 1.4 → 7.3 ± 1.4, $P = 0.011$ vs 8.9 ± 1.0 → 8.4 ± 1.2, $P = 0.036$). HbA$_{1c}$ in the TC decreased group was not different from that in the TC no change/increase group (−1.51 ± 1.30 vs −1.97 ± 2.07, $P = 0.416$).

Changes of plasma glucose and CAVI from fasting to 2 h after breakfast are shown in Figure 2. Plasma glucose levels (mg/dL) at 2 h after breakfast were significantly elevated in the DM group (143 ± 30 → 224 ± 15, $P = 0.003$) and the NDM group (78 ± 6 → 111 ± 14, $P = 0.002$). However, mean CAVI did not change in the DM group (10.4 ± 2.6 → 10.4 ± 2.5, $P = 0.836$) or the NDM group (6.6 ± 0.3 → 6.6 ± 0.3, $P = 1.000$).

DISCUSSION

The main results were as follows: (i) although ABI and IMT were not different between the DM and NDM groups, only CAVI of DM was elevated significantly compared with NDM; (ii) CAVI elevation was closely associated with HbA$_{1c}$ and aging; (iii) CAVI improved significantly as a result of the glycemic control associated with HbA$_{1c}$ improvement; and (iv) CAVI did not change before or after breakfast.

The initial two results show that the rise of CAVI is an earlier sign of arteriosclerosis than carotid ultrasonographic findings, and it is closely related to hyperglycemia. Sex differences in CAVI has been reported in a large-scale survey of healthy subjects[4]. As CAVI has been reported to be lower for females than for males, the possibility that high CAVI in DM is related to the low proportion of female DM patients cannot be fully ruled out. However, as sex was not selected as a risk factor of high CAVI by multivariate

Table 3 | Serial changes of clinical characteristics and arteriosclerotic indices before and after hospitalization in 36 diabetic patients

|	First examination	Second examination after 8 weeks	P-value
n	36	36	
Clinical characteristics			
Sex (male/female)	17/19	−	
Age (years)	58.7 ± 13.1	−	
Duration of diabetes mellitus (years)	9.1 ± 9.1	−	
Therapy (diet and exercise/OHA/insulin)	0/5/31	0/9/27	
Smoking, % (*n*/total number)	51.5 (17/33)	−	
Retinopathy, *n* (NDR/SDR/PDR)	28/5/3	−	
Nephropathy, *n* (non/micro/macro)	30/4/2	−	
Bodyweight (kg)	60.3 ± 10.9	59.8 ± 10.9	0.341
Body mass index (kg/m^2)	23.3 ± 4.0	23.2 ± 3.9	0.378
Systolic BP (mmHg)	126 ± 18	132 ± 17	0.097
Diastolic BP (mmHg)	80 ± 11	82 ± 10	0.339
HbA$_{1c}$ (%)	9.1 ± 1.8	7.4 ± 1.2	<0.001
Total cholesterol (mg/dL)	205 ± 43	185 ± 36	0.007
Triglyceride (mg/dL)	142 ± 82	145 ± 107	0.896
HDL-C (mg/dL)	48 ± 11	51 ± 14	0.256
Arteriosclerotic indices			
Right ABI	1.12 ± 0.09	1.12 ± 0.10	0.846
Left ABI	1.12 ± 0.10	1.11 ± 0.10	0.524
Mean ABI	1.12 ± 0.09	1.11 ± 0.09	0.788
Right CAVI	8.31 ± 1.33	7.84 ± 1.42	0.003
Left CAVI	8.29 ± 1.25	7.76 ± 1.44	0.001
Mean CAVI	8.30 ± 1.28	7.80 ± 1.40	0.001

Values are presented as mean ± SD. Hemoglobin A1c (HbA$_{1c}$; %) was estimated as a National Glycohemoglobin Standardization Program equivalent value. ABI, ankle brachial pressure index; BP, blood pressure; CAVI, cardio-ankle vascular index; HDL-C, high-density lipoprotein cholesterol; IMT, intima-media complex thickness; NDR, no diabetic retinopathy; OHA, oral hypoglycemic agents; PDR, proliferative diabetc retinopathy; SDR, simple diabetic retinopathy.

analyses, the contribution of sex to the high CAVI in diabetes might be low.

Increased brachial-ankle pulse wave velocity (baPWV) was also reported as an early marker of arteriosclerosis in mild hyperglycemic patients[13]. We and other investigators reported that baPWV was blood pressure dependent and was not optimal for longitudinal observation compared with CAVI[4,6]. Furthermore, several studies reported that CAVI is better than baPWV for predicting the presence of coronary
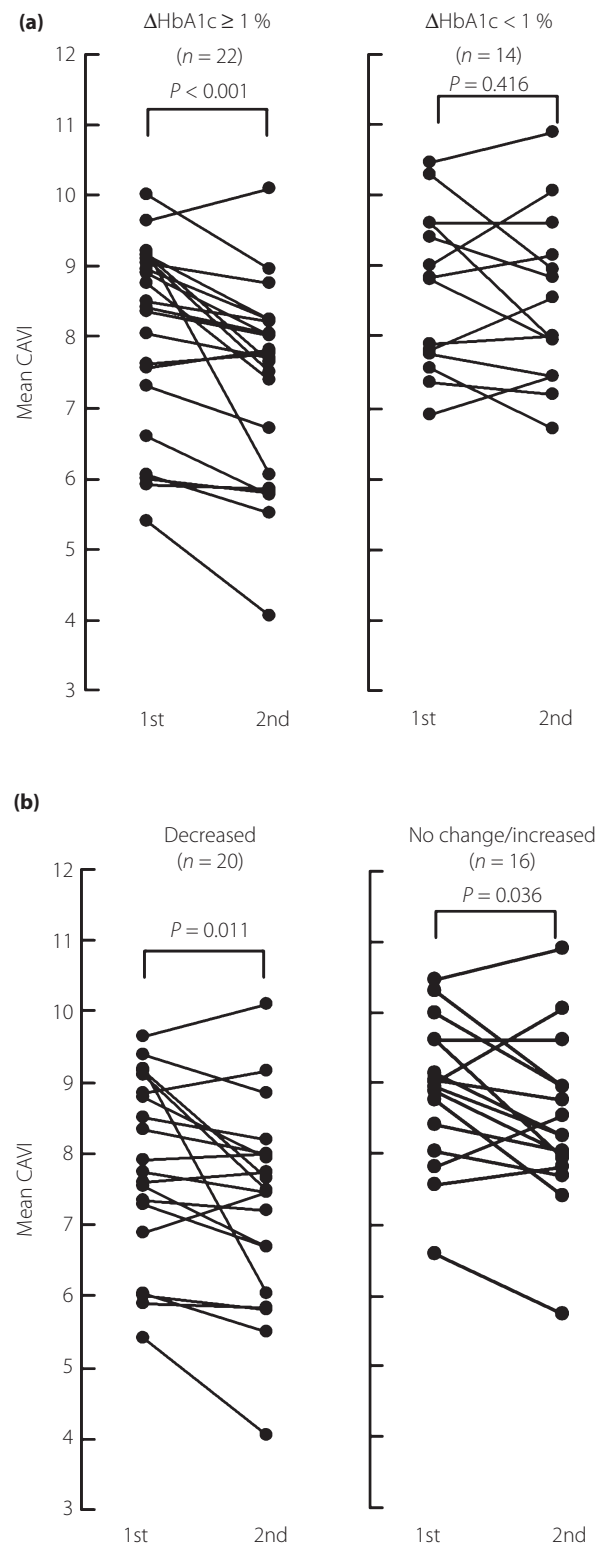
Figure 1 | Changes of cardio-ankle vascular index (CAVI) in subdivided groups by the (a) improvement of hemoglobin A1c (HbA$_{1c}$) or (b) change of total cholesterol are shown. 1st, first measurement of CAVI during hospitalization; 2nd, second measurement of CAVI after glycemic improvement.
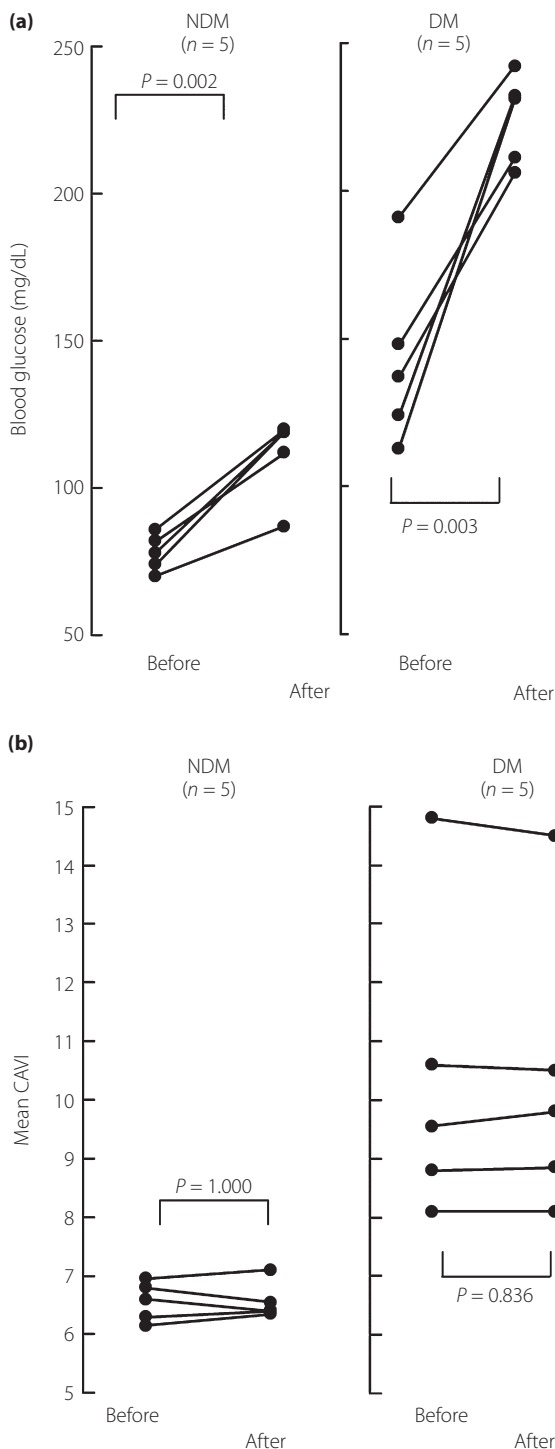
Figure 2 | Changes of (a) plasma glucose and (b) cardio-ankle vascular index (CAVI) in the diabetes mellitus (DM) and non-diabetes mellitus (NDM) groups before and after breakfast are shown.

mechanism of CAVI elevation in association with hyperglycemia remains to be elucidated. As CAVI is an index calculated by a formula including blood density[4], one possible mechanism might be an increase of blood density as a result of high blood glucose.

A third result suggests that CAVI is partially reversible by 2 months of glycemic control, mainly by insulin treatment. The present study is the first report in which CAVI improvement was closely associated with HbA$_{1c}$ improvement. When the DM patient is told that arterial stiffness is improved by strict glycemic control, the DM patient will be encouraged to self-manage good glycemic control. In contrast, a fourth result showed that a very short-term (2 h) glycemic change has no influence on CAVI. These findings might suggest that an ameliorating effect on CAVI by glycemic control is an indirect effect through changes in vascular endothelial or autonomic function, rather than a direct effect of glucose concentration.

There are a few reports in which the effect of treatment for DM on CAVI was examined. Nagayama *et al.*[19] reported that not glibenclamide, but glimepiride, improved CAVI. In that report, the change in CAVI was significantly correlated with the change in urinary 8-hydroxy-2′-deoxyguanosine, so the authors speculated that reduced oxidative stress might contribute to the improvement of CAVI. Ohira *et al.*[20] reported the amelioration of CAVI by the switching of premixed human insulin containing rapid-acting insulin to premixed insulin analog containing ultrarapid-acting insulin. Although HbA$_{1c}$ did not change during the observation period, a significant negative correlation was observed between the change in CAVI and the change in 1,5-anhydroglucitol. Therefore, the report noted, the improvement of CAVI was supposed to be elicited by the improvement of postprandial hyperglycemia.

The mechanism in which CAVI is improved by glycemic control in the present study is unknown, but the vascular endothelial and/or sympathetic nerve dysfunctions are supposed to be related to these findings. Hyperglycemia could cause endothelial dysfunction through oxidative stress, and sympathetic hyperactivity by hyperinsulinemia and dehydration. Associations between CAVI and endothelial function or alpha-adrenergic function have also been reported[21,22]. Another possible mechanism might be a decrease in blood density by glycemic control. In the present study, total cholesterol had also significantly decreased after 8 weeks of glycemic control. Although CAVI change was not closely related to the change of total cholesterol, an influence of total cholesterol could not be completely excluded from the possible mechanism of CAVI improvement. A more detailed investigation and longitudinal observation will be necessary to clarify the relationship between CAVI and diabetes mellitus.

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atherosclerosis[14–18]. Therefore, early detection of an increased arterial stiffness in the early stage of DM by CAVI might be effective for the prevention of coronary artery disease. The

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